UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/790,943	03/02/2004	William R. Wilson	093397-0501	2176

38706 7590 05/01/2009

FOLEY & LARDNER LLP
975 PAGE MILL ROAD
PALO ALTO, CA 94304

EXAMINER	
ANDERSON, JAMES D	

ART UNIT	PAPER NUMBER
1614	

MAIL DATE	DELIVERY MODE
05/01/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/790,943	WILSON ET AL.	
	Examiner	Art Unit	
	JAMES D. ANDERSON	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,7,8,11-13,16,17,20 and 21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,7,8,11-13,16,17,20 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/23/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

Applicants' response and amendments to the claims, filed 3/23/2009, are acknowledged and entered. Claims 1-4, 7-8, 11-13, 16-17, and 20-21 are pending and under examination.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/23/2009 has been entered.

Information Disclosure Statement

Receipt is acknowledged of the Information Disclosure Statement filed 3/23/2009. The Examiner has considered the references cited therein to the extent that each is a proper citation. Please see the attached USPTO Form 1449.

Claim Rejections - 35 USC § 112 – 2nd Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 7-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 7 has been amended to recite "an effective amount" of DMXAA and "an effective amount" of gemcitabine. The limitation "an effective amount" as recited in amended claim 7 renders the claims indefinite because it is not clear for what the amounts are effective or what amounts are considered by Applicants to be "effective" amounts. For example, 0.01 mg of DMXAA might be effective to inhibit a biological target *in vitro* but might not be effective to treat a subject *in vivo*. Similarly, 1,000 mg of DMXAA might have *in vivo* efficacy in the

treatment of cancer in human subject, whereas 25 mg of DMXAA might be ineffective for such treatment. Nowhere in Applicant's description of the claimed invention do they disclose amounts of DMXAA or gemcitabine intended to be incorporated into a composition. The only amounts disclosed in the specification relate to doses intended to be administered to patients having cancer, not amounts of DMXAA or gemcitabine for incorporation into a dosage form.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-4, 7-8, 11-13, 16-17 and 20-21 are rejected under 35 U.S.C. § 103(a) as being unpatentable over **Peters *et al***. (Pharmacology & Therapeutics, 2000, vol. 87, pages 227-253), **Grindley *et al***. (USP No. 5,464,826; Issued Nov. 7, 1995) and **van Moorsel *et al***. (Biochemical Pharmacology, 1999, vol. 57, pages 407-415) in view of **Siemann *et al***. (Proceedings of the American Association for Cancer Research, 2000, vol. 41, page 525) and **Pruijn *et al***. (Cancer Chemother. Pharmacol., 1997, col. 39, pages 541-546).

The instant claims are drawn to methods, compositions, and kits comprising DMXAA and gemcitabine. Dependent claims recite that the agents are in a potentiating ratio.

The Examiner previously rejected claims 1-4, 7-8, 11-13, 16-17, and 20-21 as being unpatentable over Siemann *et al*. (Proceedings of the American Association for Cancer Research,

2000, vol. 41, page 525) and Pruijn *et al.* (Cancer Chemother. Pharmacol., 1997, col. 39, pages 541-546) in view of Grindley *et al.* (USP No. 5,464,826; Issued Nov. 7, 1995) and van Moorsel *et al.* (Biochemical Pharmacology, 1999, vol. 57, pages 407-415). See Final Office Action mailed 12/22/2008 at pages 3-6. The present basis of the rejection of the claims remains the same; however the Examiner herein additionally cites Peters *et al.* who provide further teaching, suggestion, and motivation to one skilled in the art to combine antimetabolite agents such as gemcitabine with other anticancer agents for the treatment of cancer. While Applicants' arguments pertain to the previous rejection of the claims over Siemann *et al.* and Pruijn *et al.* in view of Grindley *et al.* and van Moorsel *et al.*, the Examiner will address Applicants' arguments as they relate to the new ground of rejection set forth below.

Peters *et al.* discuss the basis for combination cancer chemotherapy with antimetabolites. In this regard, Peters *et al.* teach that anticancer agents are rarely used singly to treat cancer because only a few tumors are sensitive enough to be cured by single agents. Rather, effective chemotherapy usually depends on the identification of suitable combinations to treat a specific type of tumor (page 228, left column, first paragraph). With respect to antimetabolites, Peters *et al.* teach that antimetabolites are widely used in cancer combination chemotherapy, either together with another antimetabolite or with another anticancer agent (paragraph bridging pages 231 and 232). Peters *et al.* disclose that a promising new type of combination is that of an antimetabolite with inhibitors of angiogenesis (page 233, right column). Table 1 of Peters *et al.* (page 234) discloses examples of commonly used effective combinations of antimetabolites with other anticancer agents. Table 5 of Peters *et al.* (page 244) specifically discloses combinations of gemcitabine with other anticancer agents, including 5-fluorouracil, CDDP, carboplatin, docetaxel, ifosfamide, navelbine, paclitaxel, vinorelbine, etoposide, and doxorubicin. Such combinations have been found to be effective for treating pancreatic, head and neck, mesothelioma, ovarian, bladder, NSCLC, SCLC, and breast cancers.

Grindley *et al.* is provided as further evidence that the instantly claimed gemcitabine was a compound known to be effective in treating cancer, including the instantly claimed solid tumors. In this regard, Grindley *et al.* teach a class of 2',2'-difluoronucleosides that can be used to treat neoplasms (Abstract). With respect to gemcitabine, this compound is exemplified at

column 10, lines 7-8; Table 1; and claims 2, 4-5, and 7. With respect to solid tumors, Grindley *et al.* teach that the compounds of the invention can be used to treat tumors, both solid and non-solid type (col. 16, lines 13-15). Compositions and formulations as recited in claims 7-8, 11-13, 16-17, and 20-21 are disclosed at column 16, lines 20-63.

van Moorsel *et al.* disclose combination chemotherapy studies with gemcitabine and etoposide in non-small cell lung and ovarian cancer cell lines. These antineoplastic agents are known in the art to have clinical activity against various solid tumors (Abstract). Because gemcitabine and etoposide have different mechanisms of action, the drugs were combined and studied *in vitro*. Gemcitabine has clinical activity in several solid tumors, such as ovarian cancer, NSCLC, head and neck cancer, and pancreatic cancer (page 407). Gemcitabine becomes phosphorylated to its triphosphate and is subsequently incorporated into DNA, followed by one or more deoxynucleotides after which DNA polymerization stops. Etoposide is a widely used anticancer agent that inhibits topoisomerase II (pages 407-408). Gemcitabine was solubilized in PBS for the experiments (page 408). The combined chemotherapy was shown to be synergistic in ovarian and NSCLC cells lines (Table 2). The reference thus motivates combining gemcitabine with other anticancer agents in the treatment of cancer and further demonstrates that such a combination could be synergistic in nature.

Neither Peters *et al.*, Grindley *et al.*, nor van Moorsel *et al.* disclose specifically combining gemcitabine with DMXAA as recited in the instant claims.

However, Siemann *et al.* teach that DMXAA enhances (*i.e.* potentiates) the efficacy of the chemotherapeutic agents cisplatin and cyclophosphamide in rodent (KHT sarcoma) and human (SKBR3 breast and OW1 ovarian carcinoma) tumor models. DMXAA (17.5 mg/kg) was shown to increase the tumor cell kill of cisplatin and cyclophosphamide by 10-500-fold over that seen with chemotherapy alone (Abstract). The reference thus demonstrates that DMXAA potentiates the antitumor effect of two traditional chemotherapeutic agents in a mammalian tumor model of breast and ovarian tumors.

Pruijn *et al.* also teach enhancing the antitumor activity of an anticancer agent, in this case melphalan, by co-administering melphalan with DMXAA (Abstract). DMXAA is well known in the art as an antitumor agent that inhibits tumor blood flow (page 541, right column,

"Introduction"). DMXAA is also disclosed to enhance the antitumor effects of hypoxia-selective cytotoxins (*id.*). DMXAA was formulated in phosphate-buffered saline and melphalan was dissolved in 60% propylene glycol with 40% sodium citrate and both solutions were injected *i.p.* (page 542, left column, "Materials and Methods"). The reference thus motivates one skilled in the art to formulate the compositions recited in instant claims 7-8, 11-13, 16-17, and 20-21. Figure 1 (page 543) demonstrates that DMXAA and melphalan can be administered concomitantly or sequentially and in both cases DMXAA potentiates the effect of melphalan. The reference thus expressly suggests concomitant and sequential administration as recited in claims 3-4. The reference thus expressly suggests that DMXAA can enhance the antitumor effect of a chemotherapeutic agent, likely through its inhibition of tumor blood flow which results in the entrapment of the alkylating agent caused by falling tumor blood flow (page 545, right column, last full paragraph). One skilled in the art would have been imbued with at least a reasonable expectation that DMXAA would have this effect on any known anticancer agent, including the instantly claimed gemcitabine. The authors conclude that the study demonstrates the potential of DMXAA to "induce microenvironmental changes in tumors that can be exploited by bioreductive drugs and other agents with selectivity for hypoxic and/or acidic conditions (*id.*).

Based on the combined teachings of the cited prior art, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to administer DMXAA in combination with gemcitabine as suggested and motivated by the teachings of Peters et al., Grindley *et al.* and van Moorsel *et al.* in view of the teachings of Siemann *et al.* and Pruijn *et al.* One would have been motivated to do so because each of the therapeutics instantly claimed (DMXAA and gemcitabine) have been individually taught in the prior art to be successful at treating cancer, and further, Peters *et al.*, van Moorsel *et al.*, Siemann *et al.* and Pruijn *et al.* suggest and motivate combination therapy for the treatment of cancer using DMXAA or gemcitabine and a second therapeutic agent. Accordingly, one of ordinary skill in the art would have been imbued with at least a *reasonable expectation* that gemcitabine and DMXAA in combination would be effective in treating solid tumors.

Moreover, the instant situation is amenable to the type of analysis set forth in *In re Kerkoven*, 205 USPQ 1069 (CCPA 1980) wherein the court held that it is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same

purpose. The idea of combining them flows logically from their having been individually taught in the prior art. Applying the same logic to the instant claims, one of ordinary skill in the art would have been imbued with at least a *reasonable expectation of success* that by administering DMXAA in combination with gemcitabine as suggested and motivated by the teachings of Peters et al., Grindley *et al.* and van Moorsel *et al.* in view of the teachings of Siemann *et al.* and Pruijn *et al.*, one would achieve a method of treating cancer. While *In re Kerkoven* is limited to the mechanical arts, the holdings in this case are pertinent to the present claims because the idea of combining two known anticancer drugs to treat cancer flows logically from the individual drugs being taught to be useful in treating cancer. As such, one skilled in the art would reasonably expect the combination of drugs to also be effective in treating cancer. This is especially true in the present case where the prior art teaches that combinations of DMXAA or gemcitabine with other anticancer agents having different mechanisms of action are effective to treat cancer.

Secondly, the strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. *In re Sernaker*, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983). In the present case, it is expressly recognized in the prior art that combining DMXAA or gemcitabine with other known anticancer agents would be expected to result in a composition useful for treating cancer.

Finally, it is clear from the prior art that DMXAA potentiates the antitumor effect of a number of anticancer agents (*e.g.* cisplatin, cyclophosphamide and melphalan) because of its mechanism of action (inhibiting tumor blood flow). Further, gemcitabine is clearly suggested in the prior art as a suitable compound for use in combination with other anticancer agents, including inhibitors of angiogenesis, and such combinations often provide a synergistic effect. As such, one skilled in the art would have been imbued with at least a reasonable expectation that DMXAA combined with gemcitabine would be effective as an antitumor composition.

The Examiner would like to draw Applicant's attention to the following:

"[w]hen a patent simply arranges old elements with each performing the same function it had been known to perform and yields no more than one would expect from such an arrangement, the

combination is obvious". *KSR v. Teleflex*, 127 S,Ct. 1727, 1740 (2007) (quoting *Sakraida v. A.G. Pro*, 425 U.S. 273, 282 (1976). "[W]hen the question is whether a patent claiming the combination of elements of prior art is obvious", the relevant question is "whether the improvement is more than the predictable use of prior art elements according to their established functions." (*id.*). Addressing the issue of obviousness, the Supreme Court noted that the analysis under 35 USC 103 "need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." KSR v. Teleflex, 127 S.Ct. 1727, 1741 (2007).

The Court emphasized that "[a] person of ordinary skill is... a person of ordinary creativity, not an automaton." *id* at 1742. Consistent with this reasoning, it would have been obvious to have selected various combinations of various disclosed ingredients from within a prior art disclosure, to arrive at compositions "yielding no more than one would expect from such an arrangement". In this instance since the prior art suggests and motivates a combination of DMXAA and gemcitabine for the treatment of solid tumors, it would have been obvious to one of ordinary skill in the art to select gemcitabine as an antimetabolite agent for use in combination with DMXAA and test this combination of drugs for antitumor activity.

Applicant's arguments have been carefully considered but they are not deemed to be persuasive to overcome the prima facie case of obviousness set forth *supra*.

Firstly, Applicants allege that the cited art, when combined with the knowledge of skill in the art, fails to teach or suggest the claimed invention (Arguments at page 7). In support of this argument, Applicants cite the Federal Court's decision in Takeda Chem. Indus. Ltd. v. Alphapharm Pty. Ltd., wherein the claimed 5-ethyl substituted pyridyl containing compound was held non-obvious over the closed [sic – closest] prior art compound, a 6-methyl substituted pyridyl containing compound. However, in discussing the basis for a finding of non-obviousness of the claimed compound, the court noted that the prior art taught that the compound suggested to be a lead compound for modification had undesirable side effects. The court also noted that the claimed compound exhibited unexpected efficacy without the toxicity experienced by the prior art compound. In the instant case, Applicants have neither provided any teaching away in

the prior art as it relates to the use of DMXAA and/or gemcitabine nor any demonstration of unexpected results.

Secondly, Applicants submit that the Office has failed to identify any motivation that would lead one skilled in the art to combine the cited art in a manner to achieve the claimed invention. In this regard, Applicants state that there are various anticancer agents known in the art and the prior art does not teach that gemcitabine will provide the same or better therapeutic results with any second therapeutic agent. In support of this argument, Applicants cite Exhibits I, II, and III, which disclose combinations of gemcitabine with fluorouracil (Exhibit I); vinorelbine (Exhibit II); or ralitrexed (Exhibit III). While it is true that these specific combinations were not as effective or more effective in the specific cancers they were tested in, as evidenced by Peters et al., combinations of gemcitabine with various anticancer agents having different mechanisms of action were effective in a variety of different cancers. Applicants are reminded that a guarantee of success is not the standard for obviousness. All that is required is a reasonable expectation. In view of the cited prior art, the skilled artisan would have been imbued with at least a reasonable expectation that a combination of gemcitabine and DMXAA would be effective to treat cancer.

Thirdly, Applicants refer to Exhibit IV as a demonstration that hypoxia increases resistance of human pancreatic cancer cells to apoptosis induced by gemcitabine. As cited by the Examiner, Pruijn et al. on page 545, right column, last paragraph, state, "[t]his study demonstrates the potential of DMXAA to induce microenvironmental changes in tumors that can be exploited by bioreductive drugs and other agents with selectivity for hypoxic and/or acidic conditions". As such, Applicants assert that the hypoxic conditions induced by DMXAA would increase the resistance to cancer cells to gemcitabine. However, the Examiner respectfully submits that the assays carried out in Exhibit IV were in vitro cell culture assays, wherein hypoxia was induced by incubating tumor cells in a hypoxic incubator. It is known that cells growing *in vivo* in a three-dimensional configuration have heterogeneous exposure to oxygen wherein cell growing in the center of rapidly proliferating tumors have a lower tension of oxygen, i.e., hypoxic conditions (see page 2300, left column of Exhibit IV). Such hypoxic areas are expected to exist in all tumors to some extent. As such, the fact that gemcitabine is not effective in vitro to induce apoptosis of hypoxic cells does not teach away from using

gemcitabine in combination with DMXAA to treat solid cancerous tumors. It is readily apparent from the cited prior art that both DMXAA and gemcitabine, alone or in combination with other active agents, are effective to treat such solid tumors.

Lastly, Applicants argue that they have demonstrated unexpected results. In this regard, Applicants argue that the combination of DMXAA and gemcitabine is unexpectedly superior to either agent used alone. At pages 33 and 34, Applicant's disclose results of the effects of DMXAA, gemcitabine, and DMXAA + gemcitabine in treating pancreatic tumors in vivo. The Examiner is not persuaded that the results presented in the Tables on page 34 are unexpected. In this regard, it is noted that the median number of days required for tumor volume to triple was 4.9 for the control, 6.0 for DMXAA treated tumors, 13.9 for gemcitabine treated tumors, and ">17" for DMXAA + gemcitabine treated tumors. One would expect that if the effect of DMXAA and gemcitabine were additive that the tumor volume tripling time would be about 19.9 days (6.0 + 13.9). Thus, ">17" days appears to be an expected result. Applicants argue that the Examiner should consider the treated minus control values rather than the median number of days for tumor volume to triple. Looking at this data, an additive effect would be expected to result in about 10.1 days for tumor volume tripling time whereas the combination resulted in ">12" days for the combination (treatment minus control). In the absence of statistical analysis of this data, one cannot say whether the difference between the data sets is statistically significant. However, even if the Examiner were to accept that Applicant's results are unexpected, such results are not commensurate in scope with the claims because Applicant's results are limited to pancreatic tumors whereas the claims encompass the treatment of any solid cancerous tumor.

With regard to the Declaration of Hakim Djeha, the results for combination therapy with DMXAA and gemcitabine in the treatment of lung tumors do not appear to be any different than treatment with DMXAA alone. For example, Figure 1 of said Declaration do not show a statistically significant difference in relative tumor volumes between the DMXAA and DMXAA + gemcitabine treated groups. Figure 2 also appears to show no real difference between these two treatment groups. Figure 3 clearly shows that the relative tumor volume change between DMXAA and DMXAA + gemcitabine groups is no different at 9-15 days post-treatment.

Claims 1-4, 7-8, 11-13, 16-17 and 20-21 are rejected under 35 U.S.C. § 103(a) as being unpatentable over **Davis *et al***. (WO 00/48591; Published August 24, 2000) in view of **Peters *et al***. (Pharmacology & Therapeutics, 2000, vol. 87, pages 227-253)

The instant claims are drawn to methods, compositions, and kits comprising DMXAA and gemcitabine. Dependent claims recite that the agents are in a potentiating ratio.

Davis teaches methods of inhibiting the formation of new vasculature by angiogenesis comprising administering a combination of a vasculature damaging agent and an inhibitor of the formation or action of nitric oxide in mammalian systems (Abstract).

With respect to DMXAA as recited in claims 1-4, 7-8, 11-13, 16-17, and 20-21, Davis teaches that 5,6-dimethylxanthenone acetic acid (*i.e.*, DMXAA) is a chemical compound shown to have vascular damaging activity against the newly formed endothelium of solid tumors (page 1, lines 26-27) and is exemplified as an agent useful in the invention (page 3, line 31 ; page 4, line 31).

With respect to gemcitabine as recited in claims 1-4, 7-8, 11-13, 16-17, and 20-21, Davis teaches that the vasculature damaging agent/nitric oxide inhibitor combinations disclosed therein can be administered in combination with other treatments, including antimetabolites such as 5-fluorouracil, cytosine arabinoside, and hydroxyurea (page 2, lines 27-32). For the treatment of solid tumors, the combination may be administered in combination with other anti-tumor agents (page 6, lines 20-23) and exemplifies antimetabolites (page 6, line 25) as one genus of anti-tumor agents.

With respect to concomitantly and sequentially administering DMXAA and carboplatin as recited in instant claims 3-4, Davis teaches that combination therapy may involve simultaneous or sequential application of the individual components of the treatment, thus motivating concomitant and sequential administration as instantly claimed (page 6, lines 30-32).

With respect to the compositions, pharmaceutical formulations, and kits recited in instant claims 7-8, 11-13, 16-17, and 20-21, Davis teaches the use of a composition of the invention for the preparation of a medicament for the treatment of a disease involving active angiogenesis (page 7, lines 1-3; Claims 1-10). With respect to pharmaceutically acceptable carriers and intravenous administration as recited in instant claims 11-12 and 16, Davis teaches compositions

that may include pharmaceutically acceptable excipients and compositions adapted for intravenous administration (page 5, lines 22-23 and lines 30-32).

Davis differs from the instant claims in that, while Davis discloses combining a vasculature damaging agent and nitric oxide inhibitor with antimetabolite anti-tumor agents, Davis does not explicitly disclose the claimed antimetabolite, gemcitabine.

However, Peters *et al*. discuss the basis for combination cancer chemotherapy with antimetabolites. In this regard, Peters *et al*. teach that anticancer agents are rarely used singly to treat cancer because only a few tumors are sensitive enough to be cured by single agents. Rather, effective chemotherapy usually depends on the identification of suitable combinations to treat a specific type of tumor (page 228, left column, first paragraph). With respect to antimetabolites, Peters *et al*. teach that antimetabolites are widely used in cancer combination chemotherapy, either together with another antimetabolite or with another anticancer agent (paragraph bridging pages 231 and 232). Peters *et al*. disclose that a promising new type of combination is that of an antimetabolite with inhibitors of angiogenesis (page 233, right column). Table 1 of Peters *et al*. (page 234) discloses examples of commonly used effective combinations of antimetabolites with other anticancer agents. Table 5 of Peters *et al*. (page 244) specifically discloses combinations of **gemcitabine** with other anticancer agents, including 5-fluorouracil, CDDP, carboplatin, docetaxel, ifosfamide, navelbine, paclitaxel, vinorelbine, etoposide, and doxorubicin. Such combinations have been found to be effective for treating pancreatic, head and neck, mesothelioma, ovarian, bladder, NSCLC, SCLC, and breast cancers.

Accordingly, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have combined DMXAA, a nitric oxide inhibitor, and gemcitabine in a pharmaceutical formulation for the treatment of solid tumors. The skilled artisan would have been motivated to do so because Davis suggests and motivates combining a vasculature damaging agent such as DMXAA with an inhibitor of nitric oxide synthesis for the treatment of solid tumors wherein such a combination can also be combined with an additional antitumor agent such as an antimetabolite agent. While Davis does not teach that gemcitabine as recited in the instant claims is such an antimetabolite agent, Peters et al. teach that antimetabolite agents such as gemcitabine are routinely combined with other chemotherapeutic agents and

regimens for the treatment of cancer. As such, the skilled artisan would have been imbued with at least a reasonable expectation that a combination of DMXAA, an inhibitor of nitric oxide synthesis, and gemcitabine would be effective in the treatment of solid tumors as suggested and motivated by the cited prior art.

The Examiner would like to draw Applicant's attention to the following:

"[w]hen a patent simply arranges old elements with each performing the same function it had been known to perform and yields no more than one would expect from such an arrangement, the combination is obvious". *KSR v. Teleflex*, 127 S,Ct. 1727, 1740 (2007) (quoting *Sakraida v. A.G. Pro*, 425 U.S. 273, 282 (1976). "[W]hen the question is whether a patent claiming the combination of elements of prior art is obvious", the relevant question is "whether the improvement is more than the predictable use of prior art elements according to their established functions." (*id.*). Addressing the issue of obviousness, the Supreme Court noted that the analysis under 35 USC 103 "need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." KSR v. Teleflex, 127 S.Ct. 1727, 1741 (2007).

The Court emphasized that "[a] person of ordinary skill is... a person of ordinary creativity, not an automaton." *id* at 1742. Consistent with this reasoning, it would have been obvious to have selected various combinations of various disclosed ingredients from within a prior art disclosure, to arrive at compositions "yielding no more than one would expect from such an arrangement". In this instance since the prior art teaches potentiating effects of the combination of DMXAA with an inhibitor of nitric oxide synthesis wherein such a combination can be combined with other anticancer drugs, it would have been obvious to one of ordinary skill in the art to select gemcitabine as an antimetabolite agent suggested in Davis in combination with DMXAA and an inhibitor of nitric oxide synthesis and test this combination of drugs for antitumor activity.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAMES D. ANDERSON whose telephone number is (571)272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/James D Anderson/
Examiner, Art Unit 1614

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614